REMARKS

Claims 9-11, 14, 16-20, 23, 25-28, 31 and 33-34 are pending in the application upon entry of the herein amendment. Claims 9-11 and 14-17 (Group I) stand withdrawn from consideration pursuant to a restriction requirement having been made final. Claims 12, 13, 15, 21, 22, 24, 29, 30 and 32 have been cancelled. Claims 18-20, 23, 25-28, 31 and 33-34 (Group II) are subject to examination and stand rejected. Reconsideration is requested in view of the above changes and the following remarks.

Any cancellation or amendment of claimed subject matter is without prejudice to the filing of continuing applications.

Notice of Petition Filing

Applicants give notice of the filing, on even date, of a petition seeking review of the lack of unity finding made final as between the Group I and Group II.

Discussion of Claim Amendments

Claims 18, 19 and 27 have been amended to change the recitation "specific binding member" to "an antibody or fragment thereof which binds to the cell death receptor FAS". Support is found in dependent claims 21, 22, 29 and 30, which have been cancelled. Conforming amendments have been made to claims 23, 26, 31 and 34. Claims 18, 19 and 27 have been amended to remove pemetrexed as a chemotherapeutic agent. With that amendment, claims 24 and 32 have been cancelled as redundant.

The corresponding amendments have been made to withdrawn claims 9, 10, 14 and 17. With those amendments, dependent claims 12, 13 and 15 are cancelled. The withdrawn claims have been amended in the event that the Group I claims are rejoined upon withdrawal of the lack of unity finding as between the Group I and Group II claims.

Response to Claim Objections

Claims 23 and 25 have been objected to because of the lack of recitation of a claim dependency. Claims 23 and 25 have been amended to depend from claim 18.

Response to 35 USC 112, 1st Paragraph Rejection – Lack of Enablement – Gene Therapy

Claims 18-34 were rejected as allegedly failing to comply with the enablement requirement in reciting nucleic acids encoding a binding member which binds a cell death receptor. Examiner alleges that the recitation reads on using the nucleic acids for gene therapy. Without acquiescing in the rejection, and in an effort to advance prosecution, the claims have been amended to remove reference to nucleic acids.

Response to 35 USC 112, 1st Paragraph Rejection – Lack of Enablement – Specific Binding Members

Claims 18-34 were rejected as allegedly failing to comply with the enablement requirement for a composition comprising "**any** specific binding members and/or antibody fragments".

The claims have been amended to change the recitation "specific binding member which binds to a cell death receptor" to "an antibody or fragment thereof which binds to the cell death receptor FAS". The claims, as amended, satisfy the enablement requirement of 35 USC 112.

The specification teaches that any antibody that binds FAS may be used in the invention. Many anti-FAS antibodies are known in the art, as noted by Examiner. The level of skill of those in the art is such that, given the teaching that any antibody which binds FAS may be used combined with the vast number of such antibodies known in the art, the skilled person would have no trouble in identifying additional anti-FAS antibodies or antibody molecules, which could be used in place of the exemplified CH-11. "A patent need not disclose what is well-known in the art." *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). "A patent need not teach, and preferably omits, what is well-known in the art." *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987), *cert. denied*, 108 S.Ct. 346 (1987). The specification may assume "that which is common and well-known" to persons skilled in the relevant art. *Webster Loom v. Higgins*, 105 U.S. 580 (1981).

Thus, as acknowledged by the Examiner, the disclosure of a single disclosed species may provide an adequate written description of a genus if the species disclosed is representative of the

genus; this is indeed, the situation with the anti-FAS antibody CH-11, which is representative of the genus of anti-FAS antibodies.

With regards to the reference to antibody fragments, the specification clearly teaches that antigen binding fragments of antibodies may be used in place of intact antibodies; see, for example, pages 12-15 of the description. At the time of filing the present application, it was a matter of routine skill for a person of skill in the art to use an antibody fragment in place of an intact antibody molecule which binds a particular target. The person skilled in the art would thus have no trouble in making and using antibodies and antibody fragments thereof which bind FAS, in addition to the exemplified CH-11 antibody.

The Examiner also alleges that the claims are excessively broad due to the "generic way" in which "chemotherapeutic agents" are recited. The claims are directed in this respect not to any and all chemotherapeutic agents, as Examiner implies, but to the well-defined and recognized class of chemotherapeutic agents known as topoisomerase I inhibitors. The claims are not unduly broad with respect to the chemotherapeutic agent component of the invention, in view of the state of the art, the level of skill in the art, and the teachings of the specification.

Examiner alleges at paragraphs 15 and 17 of the Detailed Action that Jiang *et al.* teaches a composition "identical to the claimed composition". This is factually incorrect, given that the composition referred to by Jiang *et al.* is merely a combination of 5-FU or cisplatin with CH-11; Jiang et al. makes no reference whatsoever to combinations of CH-11 involving topoisomerase I inhibitors.

In paragraph 18 of the Detailed Action, Examiner alleges that undue experimentation is required to practice the claimed invention, citing Gura and apparently suggesting that for claims to anti-cancer agents, *in vivo* human data is required to support such claims. The compositions of the invention are directed to combinations of (i) an antibody or antibody fragment which binds to the cell death receptor FAS, and (ii) a chemotherapeutic agent which is a topoisomerase I inhibitor. The topoisomerase I inhibitors are well-established anticancer agents used in human treatment. Their combination with antibody against FAS augments an established anticancer activity already possessed by the chemotherapeutic agent. The rationale for the rejection,

suggesting that i*n vivo* data is required, ignores this critical fact. The utility of the topoisomerase I inhibitors as anticancer agents is already well-established in the art.

Furthermore, the *in vitro* cell line data provided by the application provides sufficient workable examples and relevant data to support the claims. In this regard, Example 7 demonstrates that treatment with the topoisomerase I inhibitor CPT-11 in the HCT116 p53 null cell line results in induction of FAS (see figure 7b); Example 8 shows that CH-11 synergistically activates apoptosis in response to CPT-11 in a p53-independent manner; Example 9 illustrates that PARP cleavage and procaspase 8 activation following the addition of CH-11 is maintained following treatment with CPT-11 in a p53 null cell line; Example 10 shows that CPT-11 treatment causes a p53-independent induction of FAS cell surface expression in HCT116 p53 null cell line; Example 11 shows FAS cell surface expression in p53 mutant H630 on treatment with CPT-11; Example 12 demonstrates that the R175H and R248W p53 mutant cell lines show similar levels of FAS expression in response to CPT-11 as the isogenic HCT116 p53 null cell line. These results clearly show that topoisomerase I inhibitors act effectively (and synergistically) in combination with an anti-FAS antibody, CH-11.

Reconsideration and withdrawal of the lack of enablement rejection is respectfully requested.

Response to 35 USC 112, 1st Paragraph Rejection – Lack of Written Description

Claims 18-34 were rejected as allegedly failing to comply with the enablement requirement. The Examiner has alleged that the application does not provide adequate written description of the claimed genus of "specific binding members".

There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 191 USPQ 90, 96 (CCPA 1976). MPEP 2163 II.A. A description as filed is presumed to be adequate unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). MPEP 2163.04. The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. MPEP 2163.04.

Moreover, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986); *Capon v. Eshhar*, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005) ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge...As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution"). MPEP 2163 II.A.3.(a).

As noted above, the claims have been amended to limit the "specific binding members" to antibodies or fragments thereof which bind the death receptor FAS. The Examiner has acknowledged that the anti-FAS CH-11 antibodies fall within this claimed genus and that a single disclosed species may provide an adequate written description of the genus when the species disclosed is representative of that genus. The CH-11 antibody is, as noted above, just one of many CH-11 antibodies known in the art and would be understood by the skilled person to be representative of that genus with the selection and utilization of alternative anti-FAS antibodies being a matter of mere routine choice to one skilled in the art. Given the ease with which alternative antibodies to CH-11 can be produced, or be identified in the art, it would be unreasonable and unfair on the applicant to expect each and every alternative antibody to CH-11 to be exemplified in the present application. "[A] patent applicant does not need to include in the specification that which is already known to and available to one of ordinary skill in the art." *Koito Mfg. Co. v. Turn-Key-Tech LLC*, 72 USPQ2d 1190, 1200 (Fed. Cir. 2004).

Reconsideration and withdrawal of the lack of written description rejection is respectfully requested.

Response to 35 USC 112, 2nd Paragraph Rejection

The Examiner's objections in paragraphs 29 of the Detailed Action are now moot in view of the amendments to the claims.

Response to 35 USC 103 Rejection

The Examiner has rejected Claims 18-34 as being unpatentable over Jiang *et al.*, in view of Caligirui *et al.* and Mross *et al.* The Examiner notes that Jiang *et al.* teaches a composition comprising CH11 and 5-FU for use against hepatoma cell lines and acknowledges that it does

not teach binding members comprising human constant regions or chemotherapeutic agents which are topoisomerase I inhibitors, such as a irinotecan (CPT-11). However, the Examiner alleges that these deficiencies are remedied by Caligirui *et al.*, which allegedly teaches humanized CH11 antibodies, and Mross *et al.* which the Examiner alleges teaches that 5-FU, oxaliplatin, irinotecan and ralitrexed are "equivalent first-line anti-cancer chemotherapeutic agents".

The Examiner proceeds to assert that administration of a combination of anti-FAS antibodies in combination with chemotherapeutic agents such as 5-FU, oxaliplatin, irinotecan and ralitrexed would have been *prima facie* obvious to one of skill in the art over Jiang *et al.* in view of Caligirui *et al.* and Mross *et al.* The nub of the Examiner's argument is that 5-FU is functionally equivalent to oxaliplatin, irinotecan or ralitrexed and that the combination of any of these chemotherapeutic agents in place of 5-FU in combination with CH-11 would yield nothing more than predictable results.

It is respectfully submitted that Examiner has Examiner is over-simplified the teaching of the prior art documents. It is well recognized in the field that efficacy of drug combinations in cancer combination therapy is drug-type dependent. Indeed, the Examiner alludes to this in paragraphs 17 and 18 of the Detailed Action. 5-FU, as taught by Jiang *et al.* in combination with CH-11, is both an antimetabolite and antifolate which disrupts the folate metabolic pathway through inhibition of the enzyme thymidylate synthase, which is essential for the *de novo* synthesis of thymidine. As a uracil analogue, 5-FU also disrupts DNA and RNA synthesis through its incorporation into nucleic acid growing strands. In distinct contrast, topoisomerase I inhibitors, such as CPT-11, act by inhibition of the topoisomerase I functions of relaxing the DNA in chromatin during the S phase of the cell cycle. Topoisomerase I acts by creating DNA single strand breaks, which enable the rotation of the DNA, with uncoiled DNA being able to be replicated as it becomes accessible to the DNA synthesis machinery. Inhibition of topoisomerase I, for example by CPT-11, leads to DNA double strand breaks, eventually leading to apoptosis.

Thus, in the clinic, the use of different drug combinations results in very diverse outcomes. It is well recognized that one cytotoxic agent cannot be simply substituted for another in an efficacious regime. As another example, studies by Pectasides *et al.* show that irinotecan

and vinorelbine give a one year survival advantage in a cohort of small cell lung cancer patients over those treated with platinum based therapy (Pectasides *et al.*, 2002 *Anticancer Research*, 22:3501-3506; copy enclosed). Bearing this in mind, in contrast to the Examiner's allegation, it is not possible to predict the effect of differing cytotoxic agents in combination with an antibody such as CH-11, based on the results with other cytotoxic agents of different mechanisms of action.

In summary, it is completely incorrect to consider that 5-FU and a topoisomerase I inhibitor such as irinotecan are functionally equivalent. The agents act by a different mechanism. The efficacy of one of the chemotherapeutic agents as a single treatment therapy does not imply that its substitution with any other chemotherapeutic agent would result in a similarly efficacious effect. Moreover, indeed even more so, the efficacy of particular combination therapies are notoriously difficult to predict and the demonstration of efficacy using one particular combination regime does not imply in any way whatsoever that the substitution of one of the components of the combination regime would provide similar effects. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 USC 103.

Response to Provisional Non-Statutory Double Patenting Rejection

Claims 18-25 and 27-33 have been provisionally rejected for obviousness-type double patenting over claims 18, 19, 23, 24, 26, 30, 31 and 33 of copending application 10/514,604. Applicants defer response, as the rejection is provisional in nature because the allegedly conflicting claims have not been patented. Applicants reserve the right to respond to the rejection should the allegedly conflicting claims become patented.

Information Disclosure

An information disclosure statement is submitted herewith citing the references from the '604 application that are not already of record in the present application.

Conclusion

The claims remaining in the application are believed in condition for allowance. An early action toward that end is earnestly solicited.

Respectfully submitted,

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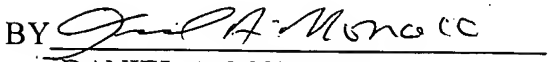
BY 

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Irinotecan and Vinorelbine in Patients with Non-small Cell Lung Cancer Previously Treated with Platinum-based Chemotherapy. A Phase II Study of the Hellenic Cooperative Oncology Group

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Abstract. *Purpose: To evaluate the efficacy and tolerability of irinotecan plus vinorelbine every 2 weeks in patients with advanced non-small cell lung cancer (NSCLC), previously treated with platinum-based chemotherapy. Patients and Methods: Forty-one patients with advanced NSCLC, refractory or resistant to platinum derivatives, were treated on an out-patient basis with irinotecan 150 mg/m^2 intravenous (i.v.) and vinorelbine 25 mg/m^2 on days 1 and 15. Chemotherapy was repeated every 4 weeks. The response was evaluated every two cycles. Results: On an intent-to-treat analysis, 6 patients (14.6 %) [95% confidence interval (CI) 5.57% to 29.17%] achieved partial response (PR), 15 (36.6%) stable disease (SD) and 20 (48.8%) progressive disease (PD). The median time to tumor progression (TTP) was 4.9 months (range 0.17-15.5 months), the median survival time was 7.8 months (range 0.9 to 19.6 months) and the 1-year survival rate was 37%. Symptomatic benefit response including improvement of performance status (PS), dyspnea, anorexia and fatigue, cessation of hemoptysis, fever and reduction of cough and pain was seen in 10 to 42% of patients. No patient experienced grade 3/4 anemia. Grade 3/4 thrombocytopenia occurred in 2 (5%) patients. Five patients (12%) developed grade 3/4 neutropenia and 5 (12%) had neutropenic fever that required hospitalization, but was successfully treated with antibiotics and G-CSF support. One patient (2%) developed grade 4 fatigue and was withdrawn. Other grade 3/4 adverse events included diarrhea (n=3; 2 required hospitalization), alopecia (n=5) and neurotoxicity (n=1). Six patients required a dose reduction. Conclusion: The combination of irinotecan plus vinorelbine administered every 2 weeks demonstrated rather low activity in advanced NSCLC patients who had previously failed platinum-based chemotherapy, but it was well-tolerated and was associated with increased 1-year survival rate and improvement in cancer related symptoms.*

Treatment options regarding second-line chemotherapy have been limited to date and, until recently, the usefulness of second-line chemotherapy for patients with metastatic non-small cell lung cancer (NSCLC) who had failed first-line chemotherapy had not been established. Any palliative treatment should be easy to administer on an out-patient basis. However, the study by Shephered *et al* (1) demonstrated the beneficial effect of chemotherapy over the best supportive care.

Over the past decade, several newer agents, such as paclitaxel, docetaxel, vinorelbine, gemcitabine, topotecan and irinotecan have demonstrated activity in patients with NSCLC with favorable toxicity profiles. Vinorelbine is a promising new cytotoxic agent which poisons the mitotic spindle and which is active in advanced NSCLC. However, variable and conflicting results have been reported in studies of second-line chemotherapy with vinorelbine. In three studies in which vinorelbine 25 mg/m^2 (2), 20 mg/m^2 (3) or 30 mg/m^2 (4) was administered weekly, no responses were reported. However, in a small 10-patient study of vinorelbine 30 mg/m^2 weekly, a 20% response rate (RR) was reported (5). The maximum tolerated dose of vinorelbine as a single agent has been established at 30-35 mg/m^2 (6).

Irinotecan inhibits the nuclear enzyme topoisomerase I, which is critical for DNA replication and transcription (7). *In vitro* studies have demonstrated the activity of irinotecan in small cell lung cancer and NSCLC cell lines (8, 9) while *in vivo* studies have documented the radiosensitizing properties of this agent in lung cancer xenografts (9). In previously untreated patients with advanced NSCLC, irinotecan has demonstrated single-agent activity comparable to that of other active agents. In a phase II trial, Fukuoka *et al* (10) reported a RR of 32% in 72 evaluable patients with previously untreated advanced NSCLC, 55% of whom had stage IV disease. The median survival was approximately 10

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Key Words: Chemotherapy, irinotecan, vinorelbine, refractory - advanced NSCLC.

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months. The main toxicity was neutropenia and diarrhea. A confirmatory trial employing a similar schedule of relatively low-dose weekly irinotecan (100 mg/m^2/weekly for 4 weeks, followed by 2 weeks of rest) reported a lower RR of 15% in 41 evaluable patients (11, 12). However, a higher percentage of patients (79%) had stage IV disease in the later trial. Like most other agents, irinotecan has produced lower RR (0-14%) in previously treated patients with NSCLC (13, 14).

In view of the activity of vinorelbine and irinotecan in NSCLC, as well as their different mechanisms of action, non-overlapping toxicity, general good tolerance and easy administration on an out-patient setting every two weeks, the Hellenic Cooperative Oncology Group (HeCOG) conducted a phase II study to evaluate the efficacy, clinical benefit and toxicity of a combination of irinotecan and vinorelbine as second-line therapy in patients with advanced NSCLC who had previously failed platinum-based chemotherapy.

Patients and Methods

Patient selection. Adult patients were enrolled in the study if they met the following criteria: cytologically or histologically confirmed diagnosis of NSCLC; measurable disease, at least one area of which had not been subject to prior irradiation; no prior therapy with irinotecan or vinorelbine: at least a four-week interval from the previous chemotherapy; performance status of 0-2 according to the Eastern Co-Operative Oncology Group (ECOG) scale; life expectancy of at least 12 weeks; adequate hematological (white blood count [WBC] >4000/mm^3, absolute granulocyte count [AGC] >1500/mm^3, platelet count > 100,000/mm^3), hepatic (bilirubin <1.5mg/dl, serum transaminases < three times the institutional upper limit of normal) and renal function (creatinine <1.5mg/dl).

Patients were not eligible for study enrollment if they had any of the following: active or uncontrolled infection; significant cardiovascular disease (uncontrolled hypertension, unstable angina, active congestive heart failure, myocardial infraction within the previous 6 months, uncontrolled serious arrhythmias); prior malignancies except for adequately treated basal cell or squamous cell skin cancer or *in situ* carcinoma of the cervix; no more than one previous chemotherapeutic regimen; pre-existing motor or sensory neurotoxicity grade >2 according to the WHO scale.

All study candidates were required to provide informed consent as approved by the local institutional ethical committee before initiation of any study procedures.

Treatment and patient evaluation. Before treatment, all eligible patients were required to provide a complete medical history and to undergo a physical examination that included assessment of weight and WHO performance status, full blood count (FBC) and biochemistry profile, electrocardiogram, chest X-rays, computed tomography scans of the thorax and abdomen and isotope bone scan.

Treatment was administered on an out-patient basis. Irinotecan plus vinorelbine therapy was administered every 2 weeks in a 4-week cycle. Irinotecan was administered at a dose of 150mg/m^2 as a 90-minute intravenous infusion and vinorelbine at a dose of 25mg/m^2 as a 15-minute intravenous infusion. Antiemetics were given at the physician's discretion. Cholinergic symptoms that occurred during or within 1 hour after receiving irinotecan were treated with atropine (1mg or as needed). Loperamide was provided as therapy for delayed diarrhea. Patients were instructed to begin taking loperamide at the first sign of diarrhea (*ie.* first poorly formed or loose stool or first episode of one to two more bowel movements than usual in day 1) that occurred more than 12 hours after irinotecan administration. Loperamide was taken in the following manner: 4mg at the first onset of diarrhea, then 2mg every 2 hours around the clock until diarrhea-free for at least 12 hours. During the night, patients were allowed to take 4mg every 4 hours.

The doses of drugs were adjusted according to WBC and platelet counts. Chemotherapy was given if the absolute granulocyte count (AGC) was ≥ 2000/μL and the platelet count was > 100,000/μL on day 1 and day 15 of treatment. Patients had a dose reduction of irinotecan to 135mg/m^2 and vinorelbine to 22.5mg/m^2 if they had an AGC nadir ≥ 1000/μL and/or platelet nadir ≥ 75,000/μL (level 1). If the AGC nadir was <500/μL and the platelet nadir <50,000/μL, irinotecan was reduced to 120mg/m^2 and vinorelbine to 20mg/m^2 (level 2). For the subsequent courses full doses of drugs were given if on the day of treatment, the AGC was ≥ 1500/μL, the platelet count ≥ 100,000/μL and any non-hematological toxicity grade was ≥2. In the event of AGC of 1000/μL to 1500/μL or platelet count of 75,000/μL to 99,000/μL, drug doses were reduced to level 1. For AGC <1000/μL or platelet count <50,000/μL, drug doses were withheld. If patients experienced a grade 3 or 4 non-hematological toxicity, the treatment was delayed until recovery to grade 1 or less and the subsequent doses were reduced to level 2. If diarrhea grade 3 or 4 occurred, the day 15 doses were omitted and the drug doses were also reduced to level 2 at subsequent doses.

Patients were evaluated on a regular basis during treatment. They were monitored for FBC and evaluated for toxicity weekly. Methods to evaluate efficacy included the tumor response rate both by "standard analysis", which considers only patients completing at least 2 cycles of therapy and by "intent to treat-analysis", which considers all patients entered in the study as evaluable, thus viewing withdrawn patients for any cause as treatment failure. Patients were also evaluated for clinical benefit response.

Standard WHO criteria (15) were used to evaluate the response to treatment and toxicities. Response evaluation was carried out after 2 cycles and/or any time when disease progression was clinically suspected. Patients were discontinued from treatment if unacceptable toxicity or rapid disease progression occurred. Patients with response or stable disease continued treatment for at least 6 cycles. Patients who were responding or stable could receive more than 6 cycles if they were achieving continued clinical benefit, as determined by the treating physician. Patients with disease progression, unacceptable toxicity and treatment delay of more than 3 weeks were taken off the study.

Statistics. The primary end-point of the study was to evaluate the response of chemotherapy while the secondary end-points were survival and toxicity.

The sample size was based on overall response rate (RR). According to Simon's two-stage minimax design, assuming that the expected overall RR would be at least 20% and the minimum acceptable response rate 5%, a sample of 13 patients would be required in the first step. Thereby if at least 4 responses occur, the probability of accepting a treatment with a real response rate of less than 5% would be 5%. On the other hand, the risk of rejecting a treatment (at the second stage) with a RR of more than 20% would be 20%. Estimates of 95% confidence intervals (CI) on RR and 1-year survival were calculated. The dose intensity for irinotecan and vinorelbine was calculated by dividing the total dose received by the number of weeks on the study.

The duration of response was calculated from the date the response was documented until the date of first progression. Survival was calculated from the day of initiation of therapy to the day of death using the Kaplan-Meier method (16). Time to tumor progression (TTP) was defined as the time elapsed from the start of the treatment to the first objective evidence of tumor progression.

Results

A total of 41 patients (36 men and 5 women) were enrolled onto the study. The patient characteristics are shown in Table

I. The median age was 58 years (range, 39-75 years). The vast majority of patients (90%) had a PS of 0 to 1. Squamous cell carcinoma and adenocarcinoma of moderate differentiation were almost equally distributed (34% and 32%, respectively). Multiple sites of disease were apparent in 36 (88%) patients, although the predominant sites of disease were the lung (58%), lymph nodes (61%), liver (41%) and bones (39%). All patients were assessable for toxicity and 37 for response. One patient withdrew his consent for the treatment after the first cycle due to severe fatigue. Three patients died soon after the initiation of chemotherapy because of rapid disease progression.

All patients had received cisplatin- or carboplatin-based chemotherapy as first-line treatment combined with taxanes (27 patients, 66%), etoposide (9 patients, 22%) and gemcitabine (5 patients, 12%). Fourteen patients (32%) (2 CRs, 12 PRs) responded to first line treatment and 18 (44%) had SD. Nine (22%) patients did not respond to cisplatin-based chemotherapy and could be considered as having cisplatin refractory disease. The median time between the completion of first-line treatment and beginning this second-line chemotherapy was 5.2 months (range 0.3-12.5 months).

On an intent-to-treat analysis the objective response rate was 14.6% (6 PRs, 95% confidence interval {CI} 5.6% to 29.2%). Fifteen patients (36.6%) achieved SD and 20 (48.8%) had PD. Of the 6 patients who achieved a PR to the irinotecan plus vinorelbine combination, 3 had a CR and 3 a PR to first-line chemotherapy. The median TTP was 4.9 months (range 0.17-15.5 months), the median survival was 7.8 months (range 0.9-19.6 months) and the 1-year survival was 37%. After a median follow-up of 13.6 months (range 0.9-19.6 months), 11 (27%) patients remained alive. The combination of irinotecan plus vinorelbine demonstrated a clinical benefit response, including reduction of dry cough in 42% of patients, pain relief in 25% with a reduction of administered analgesics, improvement of dyspnea in 30%, cessation of hemoptysis in 20%, improvement of anorexia and fatigue in 10% and disappearance of fever in 37%, respectively.

A total of 148 cycles were administered with a median of 4 cycles/patient (range 1-8 cycles/patient). The median interval between courses was 14 days (range 14-23 days). The median relative dose intensity was 90% for irinotecan and 88% for vinorelbine. Fifteen (10%) courses were delayed due to myelotoxicity, fatigue, diarrhea and neurotoxicity. Myelosupression and diarrhea were the toxicities that resulted in dose reduction (Table II). No patient had a dose reduction due to any other non-hematological toxicity. Grade 3/4 neutropenia and thrombocytopenia occurred in 5 (12%) and 2 (5%) patients, respectively. Five (12%) patients experienced febrile episodes requiring hospitalization. All episodes were successfully treated with broad-spectrum antibiotics. Eleven (27%) patients required G-CSF administration to maintain the treatment schedule. The doses were reduced in 6 (15%) patients. Grade 2/3 diarrhea was experienced by 5 (12%) patients, 2 of whom required

Table I. *Patient characteristics.*

	No	%
Number of patients	41	
Age		
Median, range	58 (39-75)	
Sex		
Male/female	36/5	88/12
PS (ECOC)*		
0	8	19
1	29	71
2	4	10
Histology		
Squamous cell	14	34
Adenocarcinoma	13	32
Large cell	2	5
Undifferentiated	10	24
Unspecified	2	5
Differentiation grade		
Well	1	2
Moderate	19	46
Poor	15	37
Unspecified	6	15
Previous surgery	8	19
Previous radiotherapy	19	46
Previous chemotherapy		
Cisplatin	22	54
Carboplatin	19	46
Taxanes	27	67
Etoposide	9	22
Gemcitabine	5	12
Sites of disease		
Lung	24	58
Pleural effusion	10	24
Lymph nodes	25	61
Liver	17	41
Bones	16	39
Brain	6	15
Adrenals	8	19
Other	10	24

*Eastern Cooperative Oncology Group

hospitalization for fluid and electrolyte replacement and treatment with loperamide. Grade 3 alopecia was noted in 5 (12%) patients. Grade 3 neurotoxicity was recorded in 1 (2%) patient. As previously mentioned, 1 patient experienced grade 4 fatigue and discontinued the treatment. There were no treatment-related deaths.

Table II. *Toxicity.*

	Patients with WHO Grade 3/4 toxicity No (%)
Neutropenia	5 (12)
Anemia	0
Thrombocytopenia	2 (5)
Alopecia	5 (12)
Neurotoxicity	1 (2)
Fatigue	1 (2)
Diarrhea	5 (12)

Discussion

Palliative chemotherapy is increasingly recognized as an important modality in advanced NSCLC. Although the use of second-line chemotherapy in advanced NSCLC is controversial, many investigators consider that symptomatic patients need some kind of treatment to achieve symptom relief. In particular, agents with good tolerability and easy administration are chosen for this particular treatment.

In an overview of treatment for recurrent NSCLC, Fossela *et al* (17), emphasized some of the difficulties of these studies. Most of them were small phase II trials, consisting of fewer than 30 patients. Frequently the details of prior treatment were not included in the report nor was the performance status of the patients. Although all studies reported RRs, very few provided median survival or 1-year survival rates. However, with the availability of new drugs there is an increasing opportunity to offer a chance of additional benefit after failure of first-line chemotherapy to these patients. Although second-line chemotherapy may induce responses in cisplatin responding patients at the time of relapse, few if any of these promising new agents have demonstrated activity in patients with cisplatin refractory NSCLC. Therefore, the identification of new chemotherapeutic agents capable of inducing response in the cisplatin refractory disease setting is of increasing importance.

In the present study the combination of two agents with different mechanisms of action and favorable toxicity profiles as single agents was explored. The primary objective of this study was to assess the efficacy and tolerability of a non-platinum regimen for NSCLC that offered the potential for simple out-patient administration along with palliation and minimal toxicity.

The combination of irinotecan and vinorelbine has been investigated as second-line treatment in advanced NSCLC (18). Cao *et al* (18) reported, in an abstract form, the results of a phase II trial combining irinotecan at a dose of 300 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1 and 15 every 28 days. Twenty-six evaluable patients with advanced NSCLC, who failed first-line chemotherapy with cisplatin, paclitaxel and gemcitabine, were included. Radiotherapy was given in 24 of them. The RR in that study was 12% and the median survival 25 weeks. The treatment was well-tolerated. Leucopenia grade 3/4 occurred in 9% of cycles and thrombocytopenia grade 2 in 3% of cycles. Grade 2 diarrhea was noted in 7% of cycles. One case of fatal toxicity with intestinal bleeding in a patient with heart disease was reported. The results from our study, which is the second phase II trial in the English literature, are consistent with those of the previous study and confirm that the combination of irinotecan and vinorelbine is safe, but with rather low efficacy. Even though results from different phase II studies have to be interpreted cautiously, second-line chemotherapy with the combination of irinotecan/vinorelbine, as given in the present study, appears to be superior to those obtained from vinorelbine, gemcitabine (19-22) and docetaxel (1, 23) monotherapy and similar to those obtained with irinotecan alone (13) or with combinations of either gemcitabine plus vinorelbine (24-27) or irinotecan plus vinorelbine (18). Furthermore, symptomatic benefit response including improvement of dyspnea, anorexia and PS, cessation of fever and hemoptysis, reduction of cough and pain with decrease of administered analgesics was seen in 10% to 42%. Despite the rather low overall RR (14.6%), treatment with this combination was associated with quite satisfactory 1-year survival. The 1-year survival of 37% appears to be better than the 19% obtained with either vinorelbine or ifosfamide (23) single-agent therapy and similar to that obtained either with taxotere (32%, 37%) (1, 23) monotherapy or with the combination of gemcitabine and vinorelbine (35%) (27) in NSCLC patients previously treated with platinum-based chemotherapy. However, the possibility that a favorable patient selection bias influenced survival in this phase II trial cannot be ruled out.

The contribution of each of these two agents, irinotecan and vinorelbine, to the activity of the regimen cannot reliably be discerned. It has been reported that about one third of chemotherapy-naive patients with advanced NSCLC respond to single agent irinotecan (28). Although irinotecan is an

active drug as second-line treatment against small cell lung cancer, two Japanese studies evaluating its efficacy as second-line treatment in NSCLC presented conflicting results (13,14). Vinorelbine has established activity as a single-agent and in combinations with cisplatin as first-line treatment (29, 30) of advanced NSCLC, but variable and conflicting results have also been reported in studies of second-line treatment (2-5). Furthermore, the activity observed in the present study as well as the study by Cao *et al* (18) might be attributed to the combined regimen.

Although there is no evidence that second-line chemotherapy can influence survival in non-responding patients or in those who experienced disease progression, it has been argued that second-line treatment may be appropriate for patients with good PS who experienced disease progression or stable disease after chemotherapy or for patients who responded to initial chemotherapy and then experienced a progression-free interval of treatment. Of the 6 PRs in our study, 3 had CR and 3 PR to first-line chemotherapy.

It has to be emphasized that the tolerability of this combination was good and the toxicity was mild. It is noteworthy that no treatment-related death occurred and the percentage of patients with severe toxicities was quite low. Grade 3/4 neutropenia and thrombocytopenia occurred in only 12% and 5% of patients; 5 (12%) patients experienced febrile episodes requiring hospitalization. All episodes were successfully treated with broad-spectrum antibiotics. The doses were reduced in 6 (15%) patients. Grade 3 diarrhea occurred in 3 (7%) patients, 2 of whom required hospitalization for fluid and electrolyte replacement and treatment with loperamide. High-dose loperamide has proved efficacious for this side-effect (31). One patient experienced grade 4 fatigue and discontinued the treatment. Alopecia grade 3 occurred in 5 (12%) patients and grade 3 neurotoxicity in 1 (2%) patient. Obviously, the use of regimens with low toxicity in this group of patients with limited prospective survival is of paramount importance.

In conclusion, irinotecan plus vinorelbine administered on a 2-week schedule to patients with previously treated advanced NSCLC showed a rather low efficacy. However, it was well-tolerated with mild toxicity and the 1-year survival achieved was high. The incidence of severe toxicities in our study was quite low and the compliance of patients to the treatment was satisfactory. Another advantage was that this combination could be easily administered on an out-patient setting. Since improvement in the outcome of patients with advanced NSCLC with second-line treatment is important, the present study adds significantly to our knowledge. Prospective randomized trials comparing this doublet combination with other doublets or with either monotherapy or best supportive care are required in order to determine the optimal treatment for this population with advanced NSCLC.

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